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CONDITIONS FOR CONFOUNDING OF THE RISK RATIO AND OF THE ODDS RATIO[1]

JEAN-FRANÇOIS BOIVIN AND SHOLOM WACHOLDER

Boivin, J-F (Dept. of Epidemiology and Health, McGill U., Montreal, Quebec, Canada H3A 2B4), and S. Wacholder. Conditions for confounding of the risk ratio and of the odds ratio. *Am J Epidemiol* 1985;121:152-8.

There are disagreements in the literature about the criteria to be used to ascertain whether or not a measure of association is confounded. The authors postulate the general principle that a crude unconfounded measure of association is structured as a weighted average of the stratum-specific values of the measure. They examine the relationships between stratum-specific measures of association, crude overall measures, and weighted averages of stratum-specific measures, and indicate how these relationships may be used to define criteria for the assessment of confounding in cohort studies in which the exposure, disease, and stratification variables are classified dichotomously. The criteria presented differ for the risk ratio and for the disease-odds ratio. In other words, one can reach different conclusions about the confounding effect of a given extraneous variable, depending on which measure of association is chosen. This view differs from that of Miettinen and Cook (Confounding: essence and detection. *Am J Epidemiol* 1981;114:593–603) who postulated *one* set of criteria for the assessment of confounding, which was applicable to *both* measures of association. These different approaches may lead to different conclusions about the presence or absence of confounding.

epidemiologic methods; statistics

A frequently encountered question in the analysis of epidemiologic data is whether a crude measure of association is confounded by the effect of an extraneous variable (1). However, there are disagreements in the literature about the criteria to be used to ascertain whether or not a measure of association is confounded. In this paper, we start from the general principle that a crude unconfounded measure of association is structured as a weighted average of the stratum-specific values of the measure. We examine the relationships between stratum-specific measures of association, crude overall measures, and weighted averages of stratum-specific measures, and indicate how these relationships may be used to define criteria for the assessment of confounding. We also extend our discussion to the question of the direction, positive or negative, of confounding effects.

NOTATION AND RESTRICTIONS

Consider a simple representation of cohort studies in which the exposure, disease, and stratification variables are all dichoto-

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Abbreviations: RR, risk ratio; AR, attributable risk.

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[1] From the Department of Epidemiology and Health, McGill University, 3775 University Street, Montreal, Quebec, Canada H3A 2B4. (Reprint requests to Dr. Jean-François Boivin.)

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mous, i.e., a 2 × 2 × 2 table. To simplify our presentation, we restrict our discussion to characteristics of expected values of estimators and, hence, do not address the issue of whether or not data-based criteria should be used in assessing confounding. In addition, we only consider the case of homogeneity of the stratum-specific measures of association. The notation is presented in tables 1 and 2.

Confounding of the Risk Ratio

A frequently used measure of association in the analysis of cohort studies is the risk ratio (RR). Using the notation presented in tables 1 and 2, the stratum-specific risk ratios (RR_i, $i = 1, 2$) are:

$$RR_i = \frac{r_{i+}}{r_{i-}} = \frac{a_i/n_i}{b_i/m_i}.$$

The crude risk ratio (RR.) can be represented as a ratio of the weighted average of the disease *risks* in the exposed subjects to the weighted average in the unexposed, with weights $(n_1/n.)$ and $(n_2/n.)$ in the numerator and $(m_1/m.)$ and $(m_2/m.)$ in the denominator, i.e.,

TABLE 1
Notation for the i^th stratum of a cohort study of the effect of a dichotomous exposure on a dichotomous disease status

Disease status	Counts* of subjects in exposure category	
	Exposed	Unexposed
Disease	a_i	b_i
No disease	c_i	d_i
All subjects	n_i	m_i

* $i = 1, 2$ for strata 1 and 2, respectively; throughout, a dot indicates summation across a subscript.

TABLE 2
Notation for risks and disease-odds

Parameter	Notation* in exposure category	
	Exposed	Unexposed
Risk	$(r_{i+}) = (a_i/n_i)$	$(r_{i-}) = (b_i/m_i)$
Disease-odds	$(o_{i+}) = (a_i/c_i)$	$(o_{i-}) = (b_i/d_i)$

* $i = 1, 2$ for strata 1 and 2, respectively; throughout, a dot indicates summation across a subscript.

$$RR. = \frac{a./n.}{b./m.} = \frac{\frac{a_1}{n_1}.\frac{n_1}{n.} + \frac{a_2}{n_2}.\frac{n_2}{n.}}{\frac{b_1}{m_1}.\frac{m_1}{m.} + \frac{b_2}{m_2}.\frac{m_2}{m.}}$$

$$= \frac{(r_{1+})(n_1/n.) + (r_{2+})(n_2/n.)}{(r_{1-})(m_1/m.) + (r_{2-})(m_2/m.)} \quad (1)$$

$$= \frac{RR_1(r_{1-})(n_1/n.) + RR_2(r_{2-})(n_2/n.)}{(r_{1-})(m_1/m.) + (r_{2-})(m_2/m.)}.$$

$$RR. = (w_1 RR_1) + (w_2 RR_2), \quad (2)$$

where

$$w_1 = \frac{(r_{1-})(n_1/n.)}{(r_{1-})(m_1/m.) + (r_{2-})(m_2/m.)}$$

and

$$w_2 = \frac{(r_{2-})(n_2/n.)}{(r_{1-})(m_1/m.) + (r_{2-})(m_2/m.)}.$$

The crude risk ratio represents a weighted average of the stratum-specific risk ratios if and only if $(w_1 + w_2) = 1$. Starting from the general principle that a crude unconfounded measure of association is structured as a weighted average of the stratum-specific values of the measure, there is no confounding of the crude risk ratio when $(w_1 + w_2) = 1$. The two situations in which this occurs are (a) $(r_{1-}) = (r_{2-})$, i.e., the risk in the unexposed is the same in the two strata. In this case, r_{1-} and r_{2-} cancel out from the numerator and denominator of w_1 and w_2; using the fact that $(n_1 + n_2) = (n.)$ and $(m_1 + m_2) = (m.)$, it can be shown that $(w_1 + w_2) = 1$. Note that since the stratum-specific risk ratios are equal, $(r_{1-}) = (r_{2-})$ implies that $(r_{1+}) = (r_{2+})$; and (b) $(n_1/n_2)/(m_1/m_2) = 1$, i.e., the stratification variable is *not* associated with the exposure among *all* study subjects, that is, unconditionally. If $(n_1/n_2)/(m_1/m_2) = 1$, then $(n_1/n.) = (m_1/m.)$ and $(n_2/n.) = (m_2/m.)$, and, therefore, $(w_1 + w_2) = 1$.

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In summary, then, when $(r_{1-}) = (r_{2-})$, or $(n_1/n_2)/(m_1/m_2) = 1$, or both, there is no confounding of the crude risk ratio. These conditions are generally well known and have been described, for example, by Kleinbaum et al. (2).

Because of the homogeneity of the stratum-specific risk ratios, equation 2 may be simplified to:

$$\mathrm{RR.} = (w_1 + w_2)\,\mathrm{RR},$$

where

$$\mathrm{RR} = \mathrm{RR}_1 = \mathrm{RR}_2.$$

Positive confounding of the crude risk ratio occurs when $(w_1 + w_2) > 1$ and negative confounding when $(w_1 + w_2) < 1$. In the case of positive confounding, the crude risk ratio is larger than the stratum-specific values, and for negative confounding, it is smaller.

The weights defined in equation 2 may be used to determine the conditions under which positive and negative confounding of the crude risk ratio occur. In general,

$$(w_1 + w_2) = \frac{(r_{1-})(n_1/n.) + (r_{2-})(n_2/n.)}{(r_{1-})(m_1/m.) + (r_{2-})(m_2/m.)}. \quad (3)$$

Positive confounding occurs if and only if the numerator of equation 3 is larger than its denominator, i.e., if and only if:

$$[(r_{1-})(n_1/n.) + (r_{2-})(n_2/n.)] > [(r_{1-})(m_1/m.) + (r_{2-})(m_2/m.)],$$

which is equivalent to

$$[(r_{1-})(n_1/n. - m_1/m.)] > [(r_{2-})(n_1/n. - m_1/m.)].$$

Some algebra shows that this inequality applies if and only if (a) the stratification variable is positively associated with both the disease and the exposure, i.e., $(r_{1-}) > (r_{2-})$ and $(n_1/n_2) > (m_1/m_2)$, or (b) the stratification variable is negatively associated with both the disease and the exposure, i.e., $(r_{1-}) < (r_{2-})$ and $(n_1/n_2) < (m_1/m_2)$.

Analogously, it can be shown that there is negative confounding of the crude risk ratio if and only if (a) $(r_{1-}) > (r_{2-})$ and $(n_1/n_2) < (m_1/m_2)$ or (b) $(r_{1-}) < (r_{2-})$ and $(n_1/n_2) > (m_1/m_2)$.

CONFOUNDING OF THE DISEASE-ODDS RATIO

Shapiro (3) showed that the structure of the crude odds ratio differs from that of the crude risk ratio. In a cohort study, the stratum-specific disease-odds ratios (OR_i, $i = 1, 2$) are:

$$\mathrm{OR}_i = \frac{o_{i+}}{o_{i-}} = \frac{a_i/c_i}{b_i/d_i}.$$

The crude odds ratio (OR.) can be represented as a ratio of the weighted average of the *odds* in the exposed subjects to the weighted average in the unexposed, with weights proportional to the numbers of subjects free of disease.

$$\mathrm{OR.} = \frac{a./c.}{b./d.} = \frac{\dfrac{a_1}{c_1}\cdot\dfrac{c_1}{c.} + \dfrac{a_2}{c_2}\cdot\dfrac{c_2}{c.}}{\dfrac{b_1}{d_1}\cdot\dfrac{d_1}{d.} + \dfrac{b_2}{d_2}\cdot\dfrac{d_2}{d.}}. \quad (4)$$

$$\mathrm{OR.} = (v_1\mathrm{OR}_1) + (v_2\mathrm{OR}_2), \quad (5)$$

where

$$v_1 = \frac{(o_{1-})(c_1/c.)}{(o_{1-})(d_1/d.) + (o_{2-})(d_2/d.)}$$

and

$$v_2 = \frac{(o_{2-})(c_2/c.)}{(o_{1-})(d_1/d.) + (o_{2-})(d_2/d.)}.$$

The crude odds ratio represents a weighted average of the stratum-specific odds ratios if and only if $(v_1 + v_2) = 1$. Using our postulate about the structure of crude unconfounded measures of association, there is no confounding of the crude odds ratio when $(v_1 + v_2) = 1$. The two situations in which this occurs are (a) $(r_{1-}) = (r_{2-})$, which is equivalent to $(o_{1-}) = (o_{2-})$; and (b) $(c_1/c_2)/(d_1/d_2) = 1$, i.e., the stratification variable is *not* associated with the exposure among the nondiseased subjects, that is, conditionally on nondisease. In

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these two cases, in parallel to what was done for equation 2, it can be shown that $(v_1 + v_2) = 1$. So, as described by Kleinbaum et al. (2), when $(r_{1-}) = (r_{2-})$, or $(c_1/c_2)/(d_1/d_2) = 1$, or both, there is no confounding of the crude odds ratio. In contrast, Miettinen and Cook (4) assess confounding of the crude odds ratio and the crude risk ratio by the same criteria, the ones we described above for the risk ratio. Thus, the Miettinen and Cook (4) approach, in contrast to ours, does not interpret confounding as a problem of weighted averages.

Because of the homogeneity of the stratum-specific odds ratios, equation 5 may be simplified to:

$$\mathrm{OR}. = (v_1 + v_2)\,\mathrm{OR},$$

where

$$\mathrm{OR} = \mathrm{OR}_1 = \mathrm{OR}_2.$$

In parallel to what was done for the risk ratio, positive and negative confounding of the crude odds ratio may be defined as confounding occurring when $(v_1 + v_2) > 1$ and $(v_1 + v_2) < 1$, respectively. Breslow and Day (5) described the conditions for positive and negative confounding of the exposure-odds ratio in case-control studies. The weights defined in equation 5 may be used to define these conditions for cohort studies, again restricting our discussion to the $2 \times 2 \times 2$ table. In general,

$$(v_1 + v_2) = \frac{(o_{1-})(c_1/c.) + (o_{2-})(c_2/c.)}{(o_{1-})(d_1/d.) + (o_{2-})(d_2/d.)}. \tag{6}$$

Positive confounding occurs if and only if the numerator of equation 6 is larger than its denominator, i.e., if and only if:

$$[(o_{1-})(c_1/c.) + (o_{2-})(c_2/c.)] > [(o_{1-})(d_1/d.) + (o_{2-})(d_2/d.)].$$

Some algebra with this inequality shows that positive confounding occurs if and only if $(r_{1-}) > (r_{2-})$ and $(c_1/c_2) > (d_1/d_2)$, or $(r_{1-}) < (r_{2-})$ and $(c_1/c_2) < (d_1/d_2)$. These criteria are the same as those for positive confounding of the risk ratio, except that the confounder-exposure association is assessed conditionally on nondisease rather than in the total population. Analogously, there is negative confounding of the crude odds ratio if and only if (a) $(r_{1-}) > (r_{2-})$ and $(c_1/c_2) < (d_1/d_2)$ or (b) $(r_{1-}) < (r_{2-})$ and $(c_1/c_2) > (d_1/d_2)$.

The discussion presented in this section deals with the disease-odds ratio, a measure of intrinsic interest in cohort studies (6). However, it is well-known that the exposure-odds ratio obtained from case-control studies is equal to the disease-odds ratio from cohort studies (7). Consequently, the conditions for positive, negative, and no confounding of the disease-odds ratio also apply to the exposure-odds ratio.

Example: risk ratio

Table 3 shows data from a hypothetical population in which the stratum-specific risk ratios are equal. The conditions for positive confounding of the crude risk ratio are present. (a) $(r_{1-}) > (r_{2-})$, i.e., the stratification variable is positively associated with the disease: $(r_{1-}) = 200/480 = 0.42 > 0.08 = 20/240 = (r_{2-})$; and (b) $(n_1/n_2) > (m_1/m_2)$, i.e., the stratification variable is positively associated with the exposure: $(n_1/n_2) = 1{,}680/264 = 6.36 > 2.00 = 480/240 = (m_1/m_2)$.

The presence of positive confounding is confirmed by inspection of table 3; the two stratum-specific risk ratios are equal to 2.00 and the crude is equal to 2.43.

Example: odds ratio

Miettinen and Cook (4) presented the hypothetical cohort data in table 4. The conditions for negative confounding of the crude odds ratio are present. (a) $(r_{1-}) > (r_{2-})$, i.e., the stratification variable is positively associated with the disease: $(r_{1-}) = 95/100 = 0.95 > 0.01 = 1/100 = (r_{2-})$; and (b) $(c_1/c_2) < (d_1/d_2)$, i.e., the stratification variable is negatively associated with the exposure among the subjects without dis-

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TABLE 3

Hypothetical data from a cohort study: homogeneity of the stratum-specific risk ratios

Stratum	Disease status	Counts of subjects in subgroup: Exposed	Counts of subjects in subgroup: Unexposed	Risk ratio	Odds ratio
1	Disease	1,400	200	2.00	7.00
	No disease	280	280		
	All subjects	1,680	480		
2	Disease	44	20	2.00	2.20
	No disease	220	220		
	All subjects	264	240		
1 + 2	Disease	1,444	220	2.43	6.56
	No disease	500	500		
	All subjects	1,944	720		

TABLE 4

Hypothetical data from a cohort study: homogeneity of the stratum-specific odds ratios, Miettinen and Cook (4)

Stratum	Disease status	Counts of subjects in subgroup: Exposed	Counts of subjects in subgroup: Unexposed	Risk ratio	Odds ratio
Male	Disease	99	95	1.04	5.21
	No disease	1	5		
	All subjects	100	100		
Female	Disease	5	1	5.00	5.21
	No disease	95	99		
	All subjects	100	100		
Male + female	Disease	104	96	1.08	1.17
	No disease	96	104		
	All subjects	200	200		

ease: $(c_1/c_2) = 1/95 = 0.01 < 0.05 = 5/99 = (d_1/d_2)$.

The presence of negative confounding is confirmed by inspection of table 4. The two stratum-specific odds ratios are equal to 5.21, and the crude is equal to 1.17.

MATCHING

The criteria defined in the previous sections for the assessment of confounding are useful for understanding some of the principles underlying the analysis of matched studies. In order to continue to restrict our discussion to the $2 \times 2 \times 2$ table, we consider frequency matching for a dichotomous variable. The results also apply to individual matching for a dichotomous variable when, as suggested by Kleinbaum et al. (2), instead of preserving the individual matches, the data are stratified for analysis according to the two categories of the matching variable. An example would be pair matching for sex, with the data presented separately for males and females, as in table 4.

The effect of frequency matching in a cohort study is to force the ratios (n_i/m_i) to be equal. In the $2 \times 2 \times 2$ table, then, $(n_1/n_2)/(m_1/m_2) = 1$, which means that, according to the criteria we defined above, there is no confounding of the crude risk ratio. It follows that when matching for a dichotomous variable has been carried out in a cohort study, the crude risk ratio is equal to the stratum-specific values. This point has already been made by Kleinbaum et al. (2), and a numerical example was given by these authors.

In contrast, even when matching is used in the selection of study subjects in a cohort

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um-specific risk ratios

	Risk ratio	Odds ratio
	2.00	7.00
	2.00	2.20
	2.43	6.56

dds ratios, Miettinen and Cook (4)

	Risk ratio	Odds ratio
	1.04	5.21
	5.00	5.21
	1.08	1.17

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study, the crude odds ratio may be confounded. The relevant sufficient condition for the absence of confounding is $(c_1/c_2)/(d_1/d_2) = 1$, but this condition will generally not be met for a frequency matching design, that is, even if $(n_1/n_2)/(m_1/m_2) = 1$. This has already been recognized implicitly by epidemiologists, especially in the analysis of case-control studies, but also in cohort and experimental studies. Even when matching has been used in the selection of the subjects, a "matched analysis" of the data is usually carried out to obtain an estimate of the odds ratio (8). The data in table 4 may be used as an example. Suppose that pair matching was carried out in the selection of study subjects, and that the data were later grouped by sex for the analysis. It might be suggested that there is no confounding of the crude odds ratio because of the equal ratio of exposed to unexposed subjects in each stratum. However, the crude odds ratio is 1.17, clearly not a weighted average of the stratum-specific values 5.21 and 5.21. According to our criteria, the crude odds ratio is confounded, and a stratified analysis such as the Mantel-Haenszel (9) procedure must be used.

Other measures of association

The attributable risk is defined as the difference between the risk of disease in the exposed and the unexposed. In the case of homogeneity of the stratum-specific attributable risks, the crude attributable risk (AR.) can be shown to be equal to:

$$AR. = AR + [(r_{1-}) - (r_{2-})](n_1/n. - m_1/m.),$$

where

$$AR = AR_1 = AR_2.$$

There is no confounding of the crude attributable risk when the term $T = [(r_{1-}) - (r_{2-})](n_1/n. - m_1/m.)$ is equal to zero. Positive and negative confounding occur when $T > 0$ and $T < 0$, respectively. It can easily be shown that the conditions for positive, negative, and no confounding in the case of homogeneity of the attributable risk are the same as those described for homogeneity of the risk ratio.

Our results for the risk ratio and the attributable risk also apply for the incidence rate ratio and incidence rate difference, respectively, replacing in our equations the total numbers of subjects n_i and m_i by the person-times at risk, and the risks r_{i+} and r_{i-} by incidence rates. Finally, the results of this paper apply for measures of association for the occurrence of *no* disease rather than of disease. This may be shown with the arguments we presented, keeping the notation identical, except that in table 1, the first row represents "No disease," and the second row "Disease."

Polychotomous stratification variables

The results given in this paper apply to the 2 × 2 × 2 table. Readers interested in the 2 × 2 × J table, $J \geq 3$, may refer to Whittemore (10) and Shapiro (3). These authors showed that the necessary conditions given here for the absence of confounding of the odds ratio and of the risk ratio are sufficient but not necessary for the 2 × 2 × J table.

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